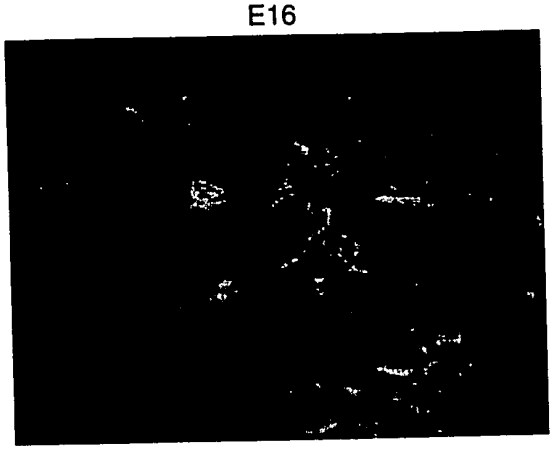


FIG. 1A

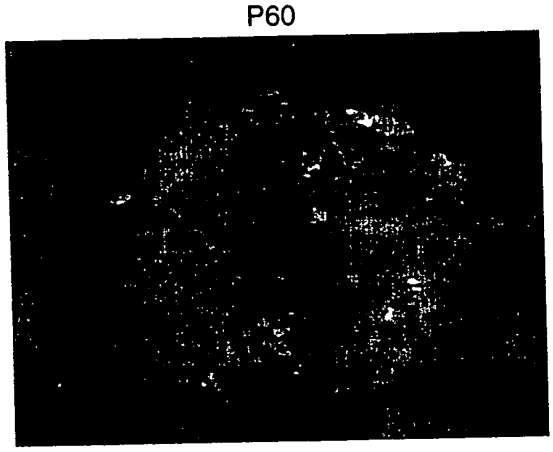
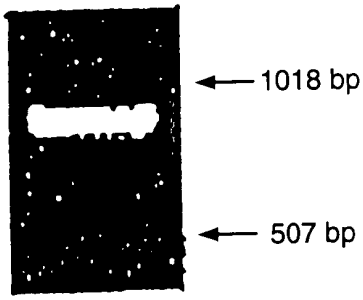


FIG. 1B



FORWARD PRIMER [GCGGGGCGGTGCGTGACTAC]
REVERSE PRIMER [GGGTGGTGAGGGTTGAGGTTTGTG]

FIG. 2

NESTIN POSITIVE CELLS PROLIFERATE AROUND ISLETS IN VITRO

FIG. 3

100x

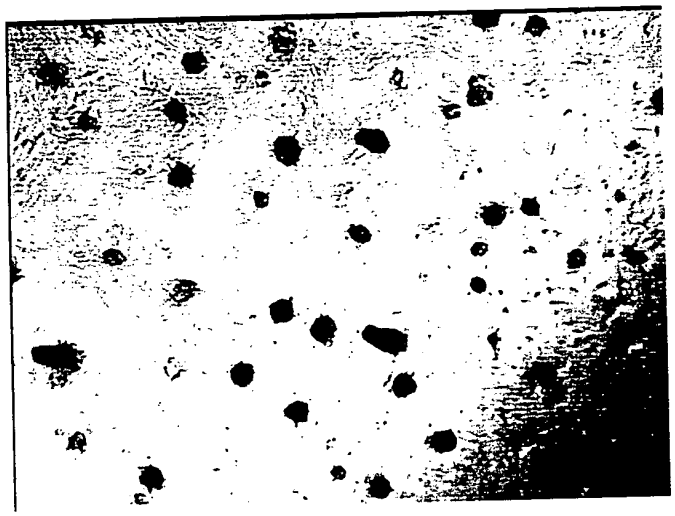


FIG. 4A

200x

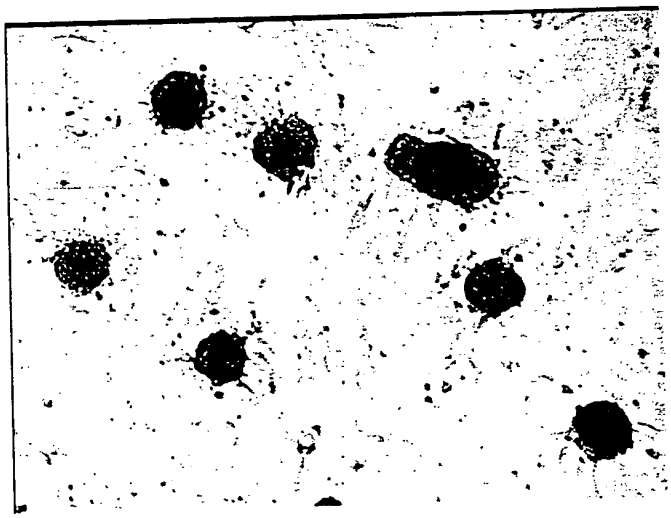


FIG. 4B

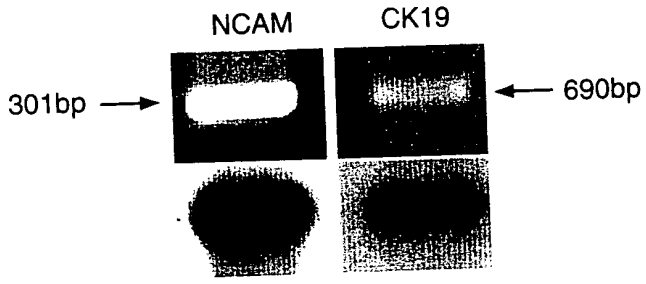


FIG. 5

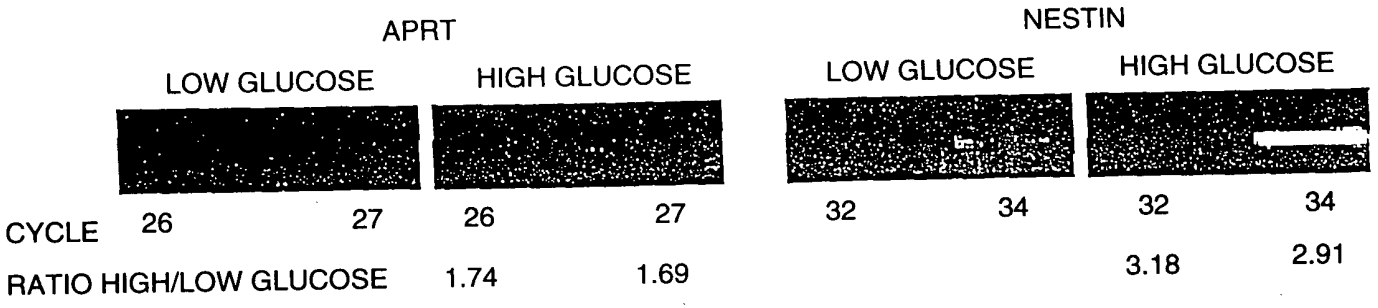


FIG. 6

Nestin Amino Acid Sequence:
"MEGCMGEESFQMWELNRRLEAYLGRVKALEEQNELLSAGLGGLR
RQSADTSWRAHADDELAALRALVDQRWREKHAAEVARDNLAEELEGVAGRCEQLRL
ARERTTEEVARNRRAVEAEKCARAWLSSQGAELERELEALRVAHEEERVGLNAQAAC
APRLPAPPRPPAPAPEVEELARRLGEAWRGAVRGYQERVAHMETSLDQTRERLARAVQ
GAR
EVRLELQQLQAERGGLLERRAALEQRLEGRWQERLRATEKFQLAVEALEQEKQGLQSQ
IAQVLEGRQQLAHLKMSLSLEVATYRTLLEAENSRLQTPGGGSKTSLSFQDPKLELQF
PRTPEGRRLGSLLPVLSPTSLPSPLPATLETPVPAFLKNQEFLQARTPTLASTPIPPT
PQAPSPAVDAEIRAQDAPLSLLQTQGGRKQAPEPLRAEARVAIPASVLPGPEEPGGQR
QEASTGQSPEDHASLAPPLSPDHSSLEAKDGESGGSRVFSICRGEGEGQIWGLVEKET
AIEGKVVSSLQQEIWEEEDLNRKEIQDSQVPLEKETLKSLGEEIQESLKTLENQSHET
LERENQECPRSLEEDLETLKSLEKENKRAIKGCGGSETSRKRGCRQLKPTGKEDTQTL
QSLQKENQELMKSLEGNLETFLFPGTENQELVSSLQENLESLTALEKENQEPLRSPEV
GDEEALRPLTKENQEPLRSLEDENKEAFRSLEKENQEPLKTLEEEDQSIVRPLETENH
KSLRSLEEQDQETLRTLEKETQQRRRSLGEQDQMTLRPPEKVDLEPLKSLDQEIARPL
ENENQEFLKSLKEESVEAVKSLETEILESLKSAGQENLETLKSPETQAPLWTPEEINK
SGGNESSRKGNSRTTGVCGSEPRDIQTPGRGESGIIEISGSMEPGEFEISRGVDKESQ
RNLEEEENLGKGEYQESLRSLEEEGQELPQSADVQRWEDTVEKDQELAQESPPGMAGV
ENKDEAELNLREQDGFTGKEEVVEQGELNATEEVWFPGEGHPENPEPKEQRGLVEGAS
VKGGAEGLQDPEGQSQQVGTPGLQAPQGLPEAIEPLVEDDVAPGGDQASPEVMLGSEP
AMGESAAGAEPGLGQGVGGLGDPGHLTREEVMEPPLEEESLEAKRVQGLEGPRKDLEE
AGGLGTEFSELPGKSRDPWEPPREGREESEAEAPRGAEEAFPAETLGHTGSDAPSPWP
LGSEEAEEDVPPVLVSPSPTYTPILEDAPGLQPQAEGSQEASWGVQGRAEAGKVESEQ
EELGSGEIPEGLQEEGEESREESEEDELGETLPDSTPLGFYLRSPTSPRWTPLESRGH
PLKETGKEGWDPAVLASEGLEEPSEKEEGEEGEEECGRDSDLSEEFEDLGTEAPFLPG
VPGEVAEPLGQVPQLLLDPAAWDRDGESDGFADEEESGEEGEEDQEEGREPGAGRWGP
GSSVGSLQALSSSQRGEFLESDSVSVSVPWDDSLRGAVAGAPKTALETESQDSAEPSG
SEEESDPVSLEREDKVPGPLEIPSGMEDAGPGADIIGVNGQGPNLEGKSQHVNGGVMN
GLEQSEESGARNALVSEGDRGSPFQEEEGSALKRSSAGAPVHLGQGQFLKFTQREGDR
ESWSSGED"

Nestin Nucleotide Sequence:
BASE COUNT 1238 a 1176 c 1676 g 764 t ORIGIN 1
atggagggct gcatggggga ggagtcgttt cagatgtggg agctcaatcg gcgcctggag 61
gcctacctgg gccgggtcaa ggcgctggag gagcagaatg agctgctcag cgccggactc 121
gggggctcc ggcgacaatc cgcggacacc tcctggcggg cgcatgccga cgacgagctg 181
gcggccctgc gtgcgctcgt tgaccaacgc tggcgggaga agcacgcggc cgaggtggcg 241
cgcgacaacc tggctgaaga gctggagggc gtggcaggcc gatgcgagca gctgcggctg 301
gcccgggagc ggacgacgga ggaggtagcc cgcaaccggc gcgccgtcga ggcagagaaa
361 tgcgcccggg cctggctgag tagccagggg gcagagctgg agcgcgagct agaggctcta
421 cgcgtggcgc acgaggagga gcgcgtcggt ctgaacgcgc aggctgcctg tgccccccgc

FIG. 7A

481 ctgcccgcgc cgccccggcc tcccgcgccg gccccggagg tagaggagct ggcaaggcga
541 ctgggcgagg cgtggcgcgg ggcagtgcgc ggctaccagg agcgcgtggc acacatggag
601 acgtcgctgg accagacccg cgagcgcctg gcccgggcgg tgcagggtgc ccgcgaggtc
661 cgcctggagc tgcagcagct ccaggctgag cgcggaggcc tcctggagcg cagggcagcg
721 ttggaacaga ggttggaggg ccgctggcag gagcggctgc gggctactga aaagttccag
781 ctggctgtgg aggccctgga gcaggagaaa cagggcctac agagccagat cgctcaggtc
841 ctggaaggtc ggcagcagct ggcgcacctc aagatgtccc tcagcctgga ggtggccacg
901 tacaggaccc tcctggaggc tgagaactcc cggctgcaaa cacctggcgg tggctccaag
961 acttccctca gctttcagga ccccaagctg gagctgcaat tccctaggac cccagagggc
1021 cggcgtcttg gatctttgct cccagtcctg agcccaactt ccctcccctc acccttgcct
1081 gctacccttg agacacctgt gccagccttt cttaagaacc aagaattcct ccaggcccgt
1141 acccctacct tggccagcac ccccatcccc cccacacctc aggcaccctc tcctgctgta
1201 gatgcagaga tcagagccca ggatgctcct ctctctctgc tccagacaca gggtgggagg
1261 aaacaggctc cagagccccc gcgggctgaa gccagggtgg ccattcctgc cagcgtcctg
1321 cctggaccag aggagcctgg gggccagcgg caagaggcca gtacaggcca
gtccccagag 1381 gaccatgcct ccttggcacc acccctcagc cctgaccact ccagtttaga
ggctaaggat 1441 ggagaatccg gtgggtctag agtgttcagc atatgccgag gggaaggtga
agggcaaatc 1501 tgggggttgg tagagaaaga aacagccata gagggcaaag tggtaagcag
cttgcagcag 1561 gaaatatggg aagaagagga tctaaacagg aaggaaatcc aggactccca
ggttcctttg 1621 gaaaaagaaa ccctgaagtc tctgggagag gagattcaag agtcactgaa
gactctggaa 1681 aaccagagcc atgagacact agaaagggag aatcaagaat gtccgaggtc
tttagaagaa 1741 gacttagaaa cactaaaaag tctagaaaag gaaaataaaa gagctattaa
aggatgtgga 1801 ggtagtgaga cctctagaaa aagaggctgt aggcaactta agcctacagg
aaaagaggac 1861 acacagacat tgcaatccct gcaaaaggag aatcaagaac taatgaaatc
tcttgaaggt 1921 aatctagaga catttttatt tccaggaacg gaaaatcaag aattagtaag
ttctctgcaa 1981 gagaacttag agtcattgac agctctggaa aaggagaatc aagagccact
gagatctcca 2041 gaagtagggg atgaggaggc actgagacct ctgacaaagg agaatcagga
acccctgagg 2101 tctcttgaag atgagaacaa agaggccttt agatctctag aaaaagagaa
ccaggagcca 2161 ctgaagactc tagaagaaga ggaccagagt attgtgagac ctctagaaac
agagaatcac 2221 aaatcactga ggtctttaga agaacaggac caagagacat tgagaactct
tgaaaaagag 2281 actcaacagc gacggaggtc tctaggggaa caggatcaga tgacattaag
acccccagaa 2341 aaagtggatc tagaaccact gaagtctctt gaccaggaga tagctagacc
tcttgaaaat 2401 gagaatcaag agttcttaaa gtcactcaaa gaagagagcg tagaggcagt
aaaatcttta 2461 gaaacagaga tcctagaatc actgaagtct gcgggacaag agaacctgga
aacactgaaa 2521 tctccagaaa ctcaagcacc actgtggact ccagaagaaa taaataaatc
agggggcaat 2581 gaatcctcta gaaaaggaaa ttcaagaacc actggagtct gtggaagtga
accaagagac 2641 attcagactc ctggaagagg agaatcagga atcattgaga tctctgggag
catggaacct 2701 ggagaatttg agatctccag aggagtagac aaggaaagtc aaaggaatct
ggaagaggaa 2761 gagaacctgg gaaagggaga gtaccaagag tcactgaggt ctctggagga
ggagggacag 2821 gagctgccgc agtctgcaga tgtgcagagg tgggaagata cggtggagaa
ggaccaagaa 2881 ctggctcagg aaagccctcc tgggatggct ggagtggaaa ataaggatga
ggcagagctg 2941 aatctaaggg agcaggatgg cttcactggg aaggaggagg tggtagagca
gggagagctg 3001 aatgccacag aggaggtctg gttcccaggc gaggggcacc

FIG. 7B

cagagaaccc tgagcccaaa 3061 gagcagagag gcctggttga gggagccagt
gtgaagggag gggctgaggg cctccaggac 3121 cctgaagggc aatcacaaca
ggtggggacc ccaggcctcc aggctcccca ggggctgcca 3181 gaggcgatag agcccctggt
ggaagatgat gtggccccag ggggtgacca agcctcccca 3241 gaggtcatgt tggggtcaga
gcctgccatg ggtgagtctg ctgcgggagc tgagccaggc 3301 ctggggcagg gggtgggagg
gctgggggac ccaggccatc tgaccaggga agaggtgatg 3361 gaaccacccc
tggaagagga gagtttggag gcaaagaggg ttcagggctt ggaagggcct 3421 agaaaggacc
tagaggaggc aggtggtctg gggacagagt tctccgagct gcctgggaag 3481 agcagagacc
cttgggagcc tcccagggag ggtagggagg agtcagaggc tgaggccccc 3541
aggggagcag aggaggcgtt ccctgctgag accctgggcc acactggaag tgatgcccct 3601
tcaccttggc ctctggggtc agaggaagct gaggaggatg taccaccagt gctggtctcc 3661
cccagcccaa cgtacacccc gatcctggaa gatgcccctg ggctccagcc tcaggctgaa 3721
gggagtcagg aggctagctg gggggtgcag gggagggctg aagctgggaa agtagagagc 3781
gagcaggagg agttgggttc tggggagatc cccgagggcc tccaggagga aggggaggag 3841
agcagagaag agagcgagga ggatgagctc ggggagaccc ttccagactc cactcccctg 3901
ggcttctacc tcaggtcccc cacctccccc aggtggaccc cactggagag cagaggccac 3961
cccctcaagg agactggaaa ggagggctgg gatcctgctg tcctggcttc cgagggcctt 4021
gaggaaccct cagaaaagga ggagggggag gagggagaag aggagtgtgg ccgtgactct
4081 gacctgtcag aagaatttga ggacctgggg actgaggcac cttttcttcc tggggtccct
4141 ggggaggtgg cagaacctct gggccaggtg ccccagctgc tactggatcc tgcagcctgg
4201 gatcgagatg gggagtctga tgggtttgca gatgaggaag aaagtgggga ggagggagag
4261 gaggatcagg aggaggggag ggagccaggg gctgggcggt gggggccagg gtcttctgtt
4321 ggcagcctcc aggccctgag tagctcccag agaggggaat tcctggagtc tgattctgta
4381 agtgtcagcg tcccctggga tgacagcttg aggggtgcag tggctggtgc ccccaagact
4441 gccctggaaa cggagtccca ggacagtgct gagccttctg gctcagagga agagtctgac
4501 cctgtttcct tggagaggga ggacaaagtc cctggccctc tagagatccc cagtgggatg
4561 gaggatgcag gcccaggggc agacatcatt ggtgttaatg gccagggtcc caacttggag
4621 gggaagtcac agcatgtaaa tgggggagta atgaacgggc tggagcagtc tgaggaaagt
4681 ggggcaagga atgcgctagt ctctgaggga gaccgaggga gccccttca ggaggaggag
4741 gggagtgctc tgaagaggtc ttcggcaggg gctcctgttc acctgggcca gggtcagttc
4801 ctgaagttca ctcagaggga aggagataga gagtcctggt cctcagggga ggac //

FIG. 7C

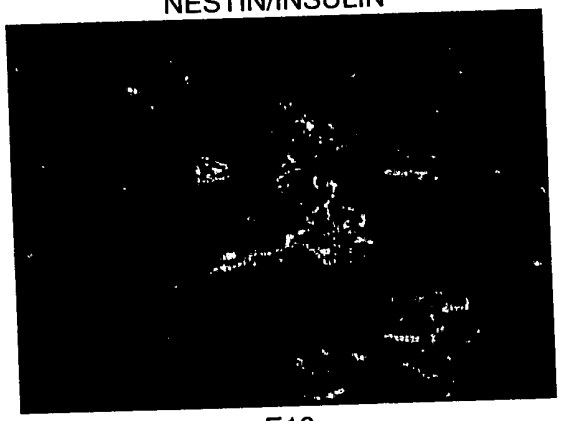


FIG. 8A

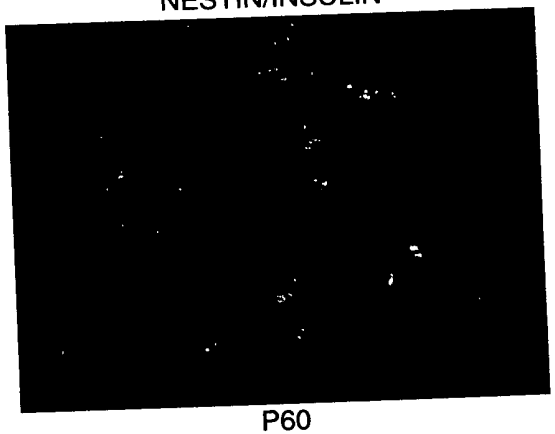


FIG. 8B

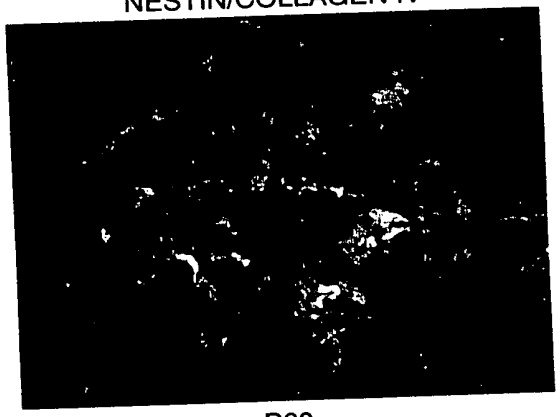


FIG. 8C

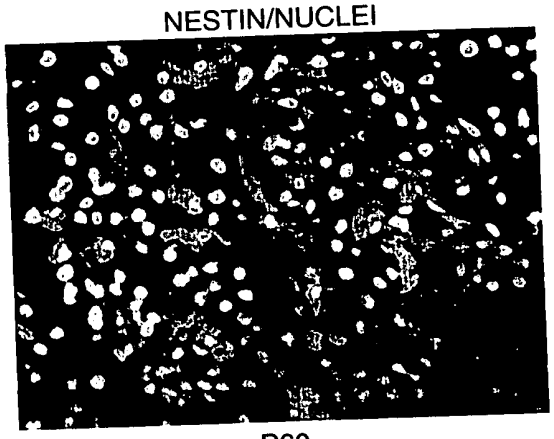


FIG. 8D

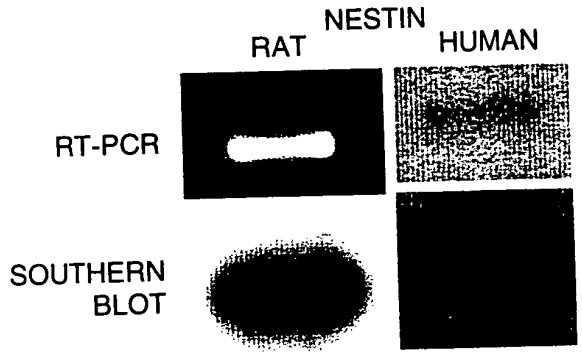


FIG. 8E

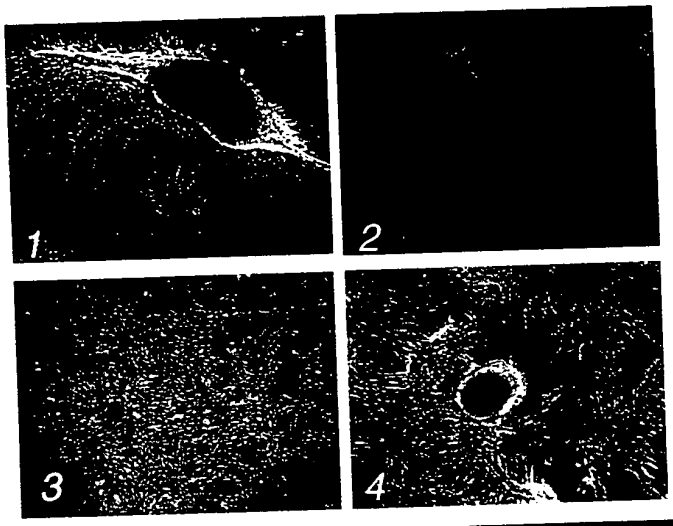


FIG. 9A

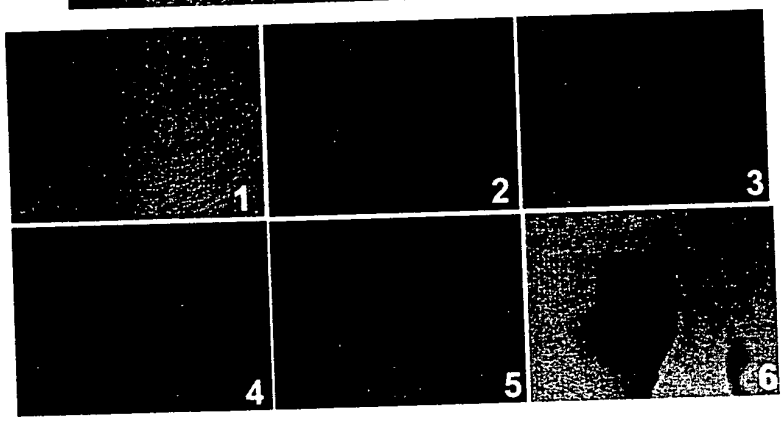


FIG. 9B

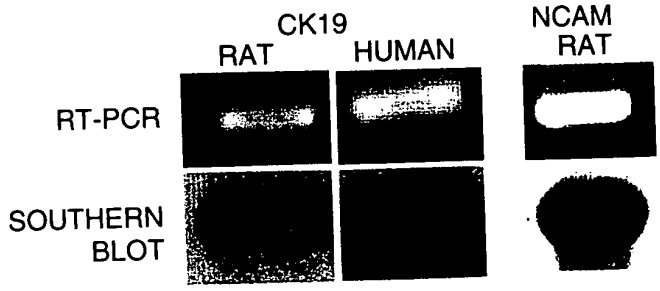


FIG. 9C

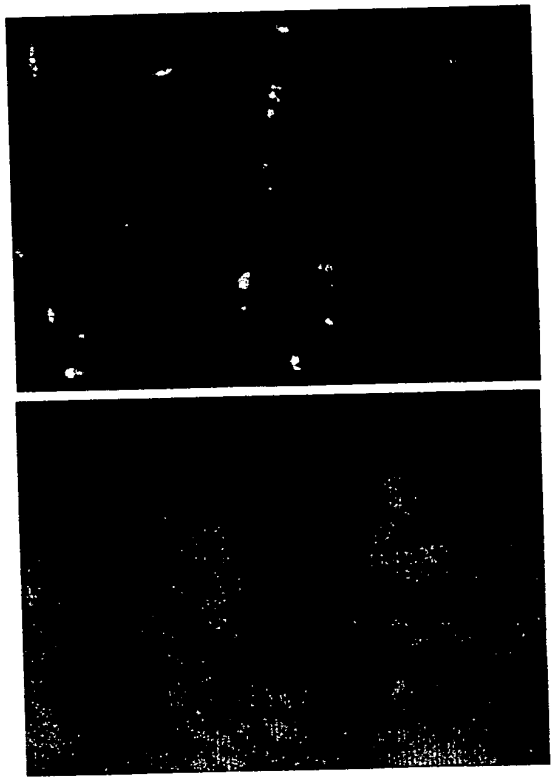


FIG. 10A

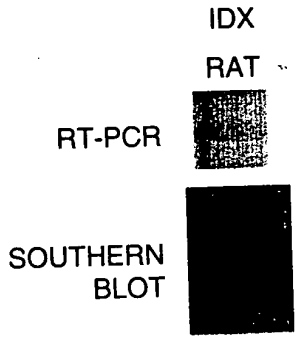


FIG. 10B

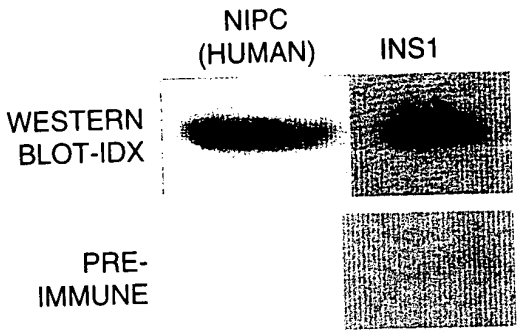


FIG. 10C

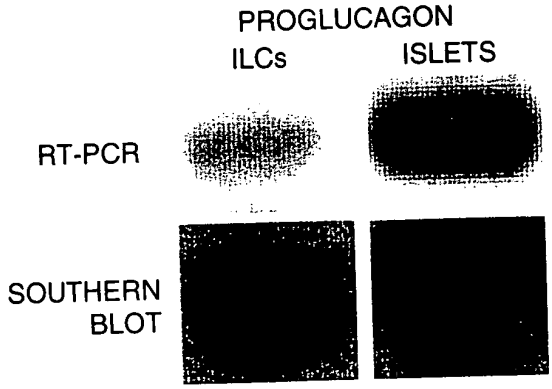


FIG. 10D

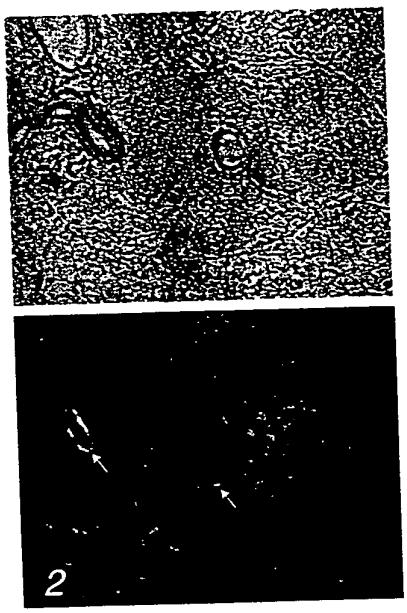


FIG. 11A

FIG. 11B

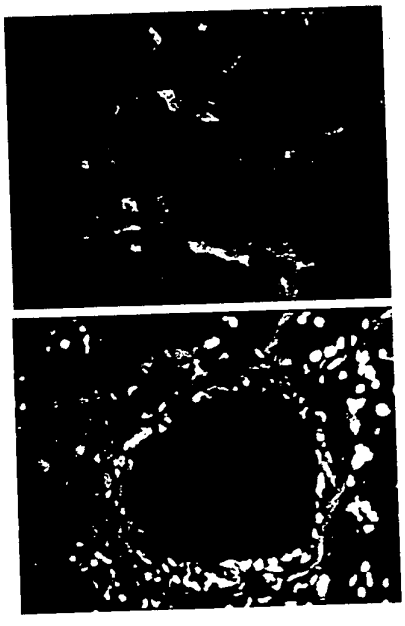


FIG. 11C

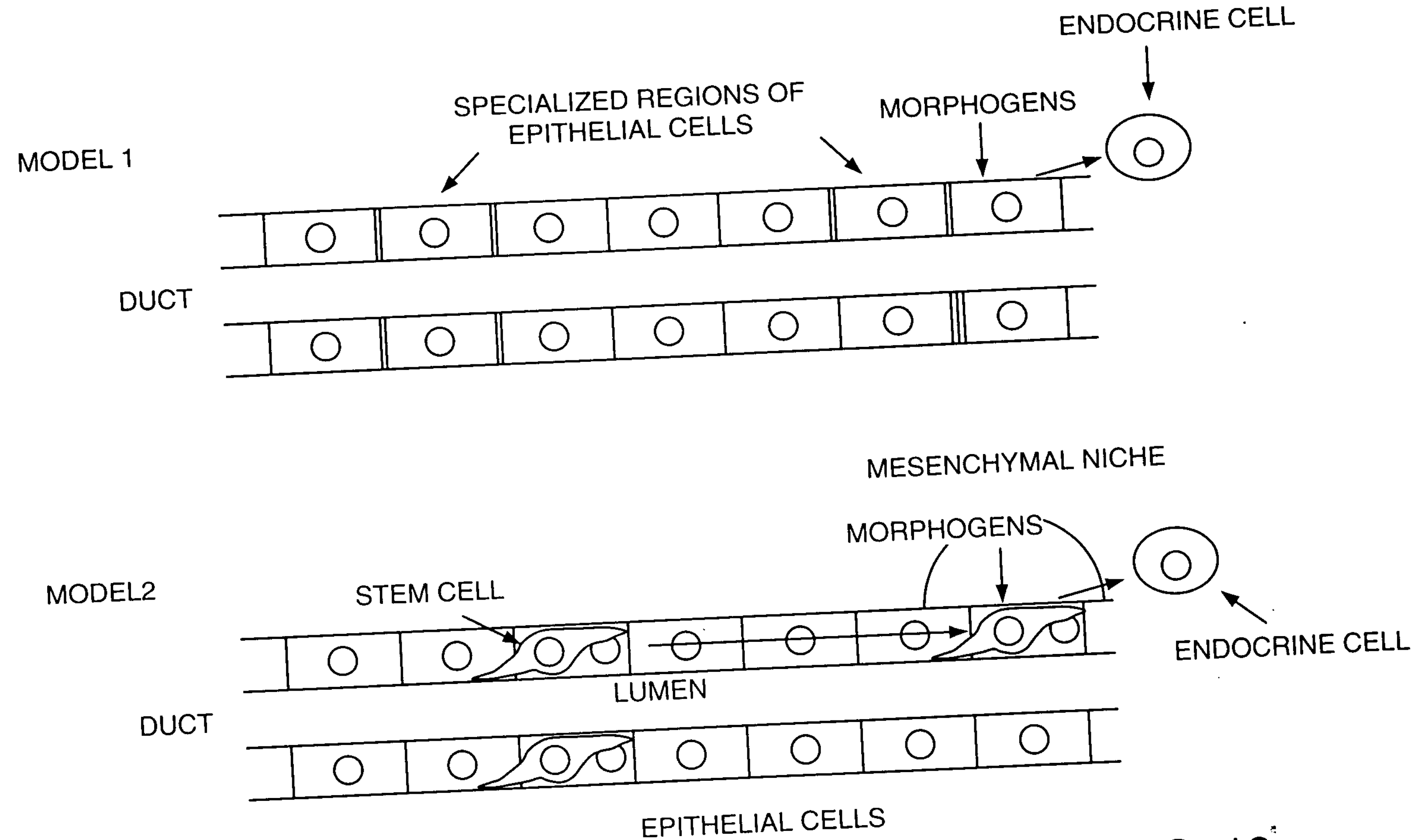

MODEL 1
SPECIALIZED REGIONS OF
EPITHELIAL CELLS
MORPHOGENS
ENDOCRINE CELL
DUCT
MODEL2
MESENCHYMAL NICHE
MORPHOGENS
STEM CELL
ENDOCRINE CELL
LUMEN
DUCT
EPITHELIAL CELLS

FIG. 12

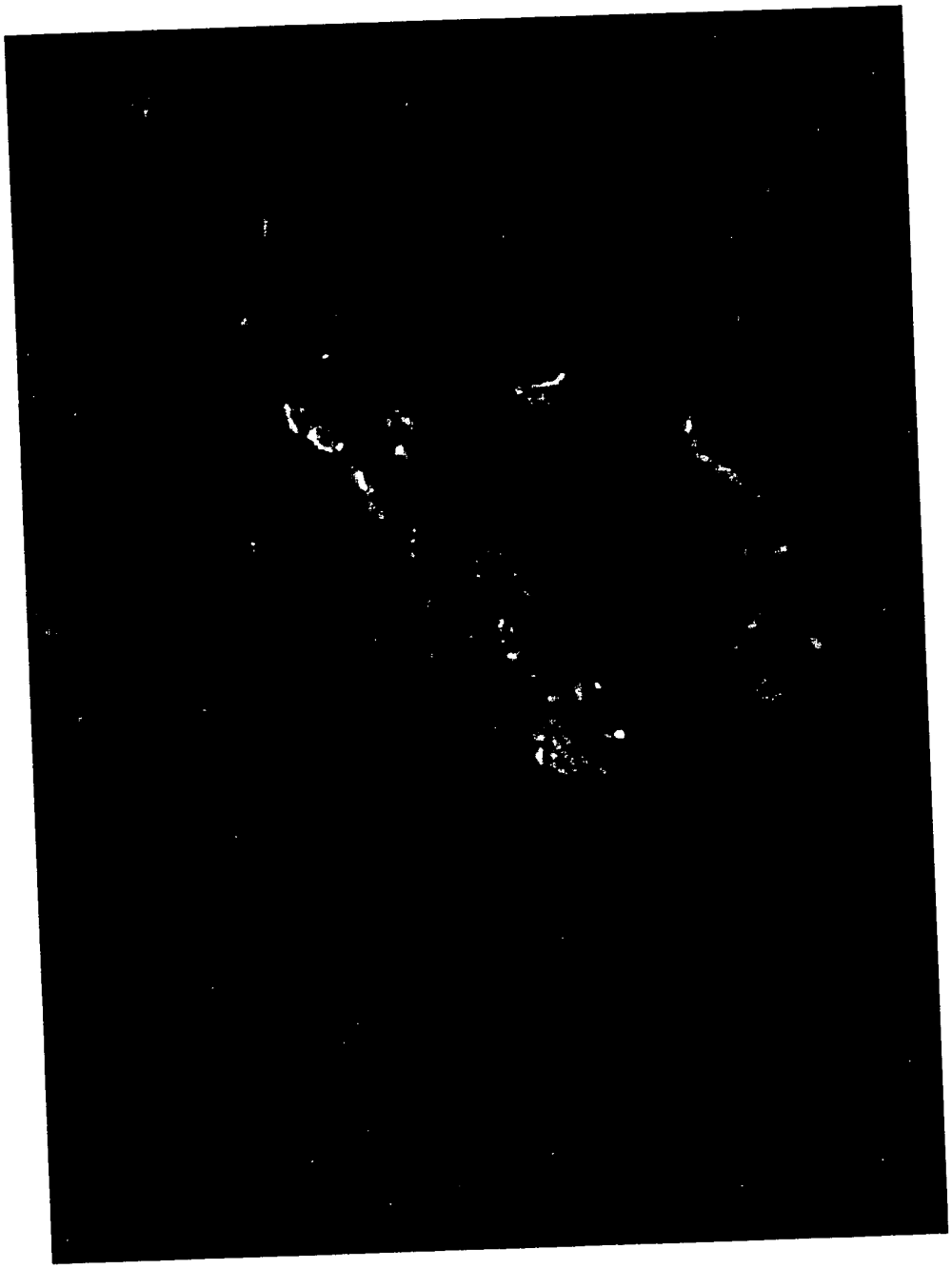


FIG. 13A

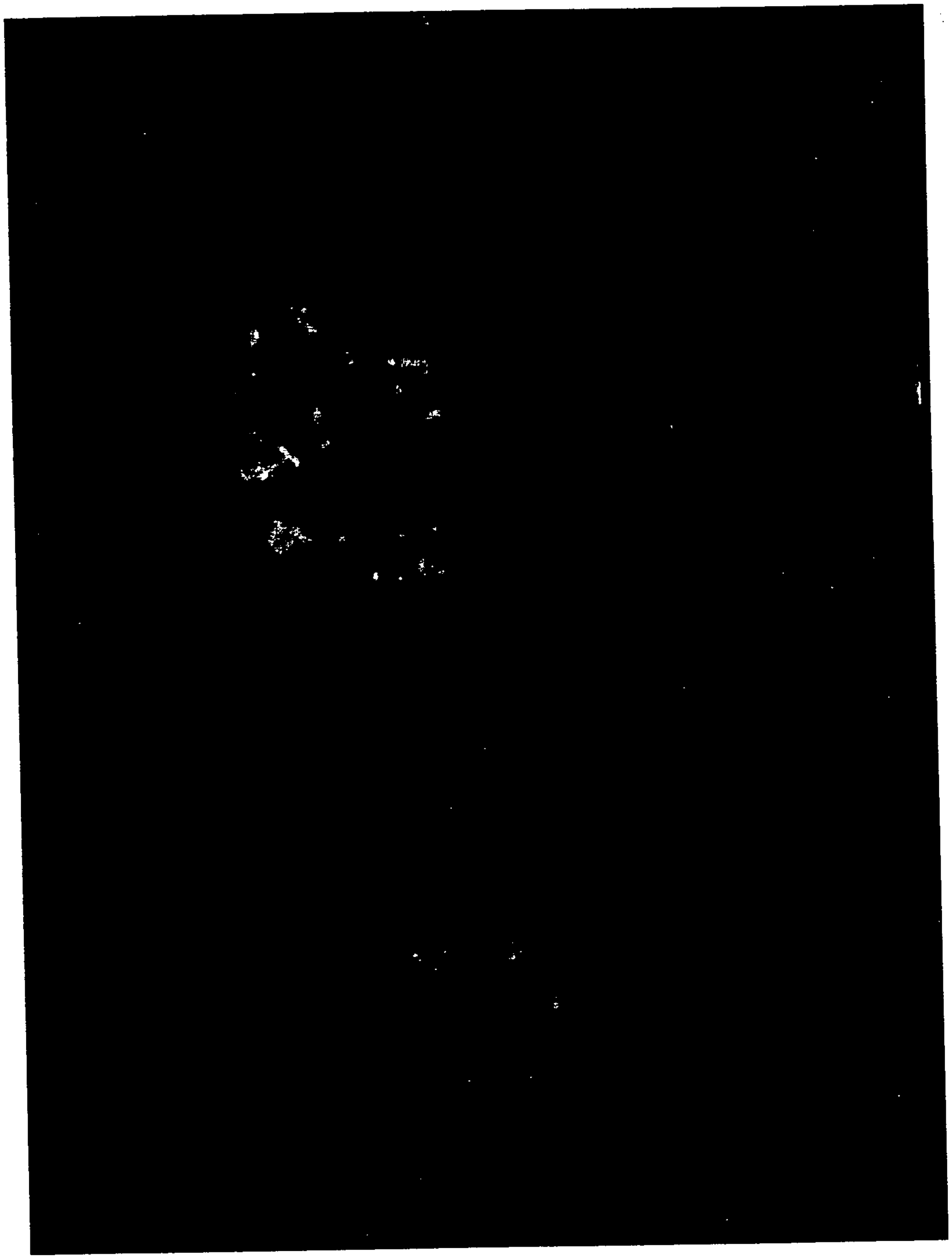


FIG. 13B

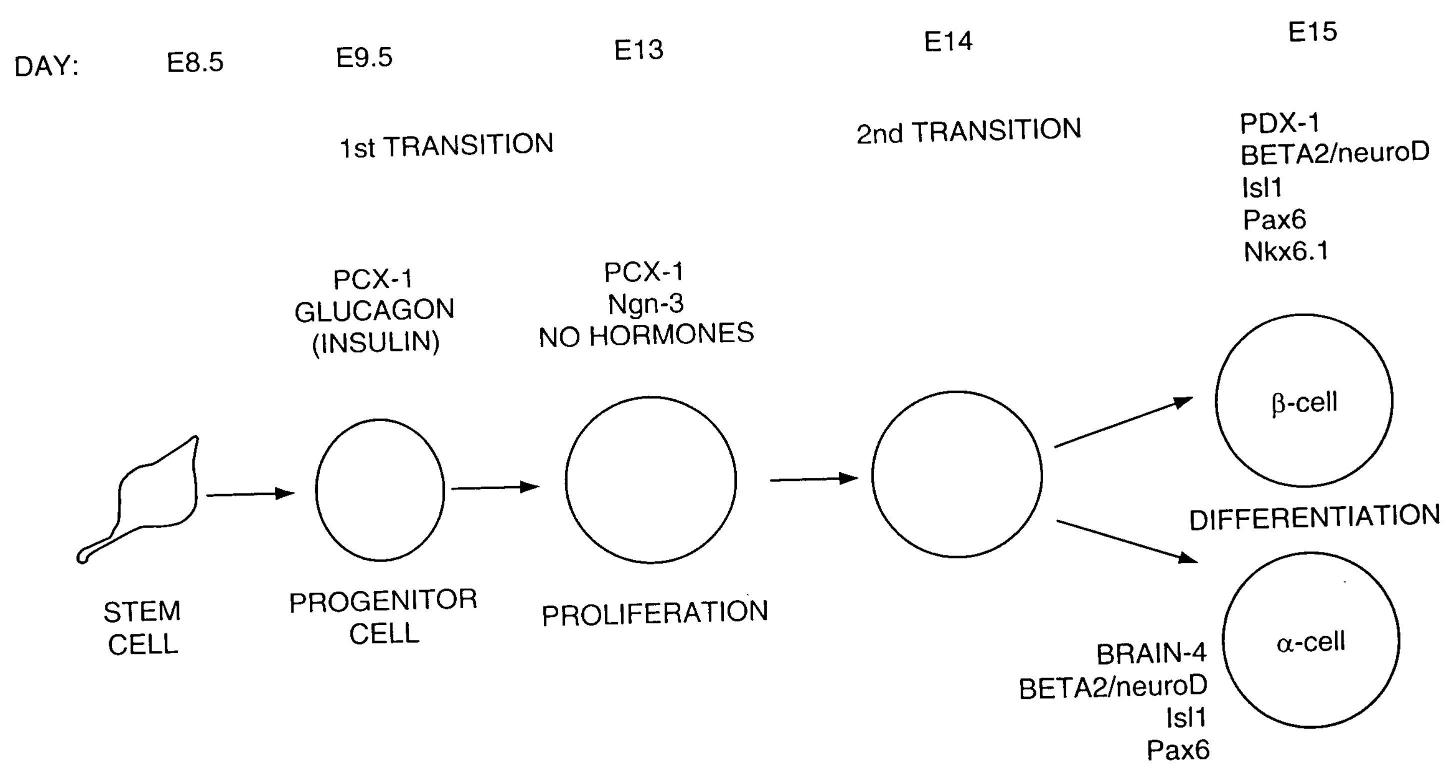

DAY:
E8.5
E9.5
E13
E14
E15
1st TRANSITION
2nd TRANSITION
PDX-1
BETA2/neuroD
Isl1
Pax6
Nkx6.1
PCX-1
GLUCAGON
(INSULIN)
PCX-1
Ngn-3
NO HORMONES
β-cell
DIFFERENTIATION
α-cell
STEM
CELL
PROGENITOR
CELL
PROLIFERATION
BRAIN-4
BETA2/neuroD
Isl1
Pax6

FIG. 14

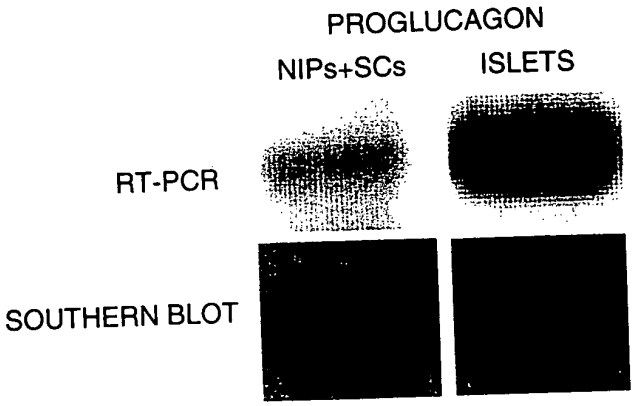


FIG. 15A

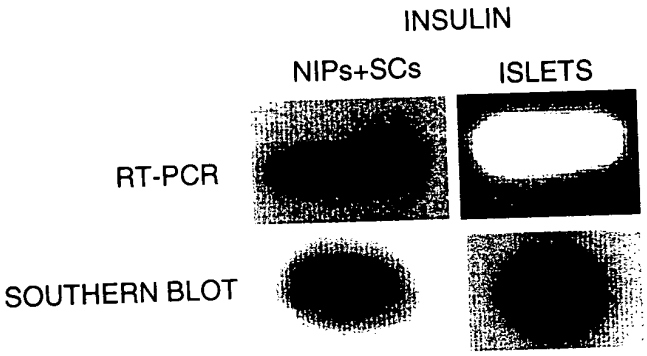


FIG. 15B

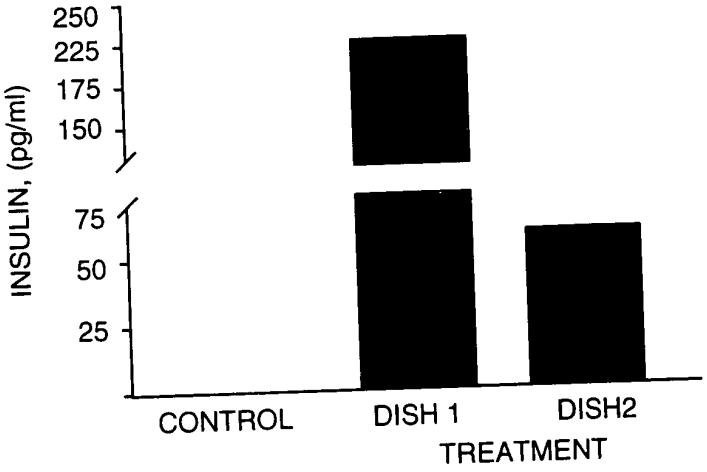


FIG. 15C

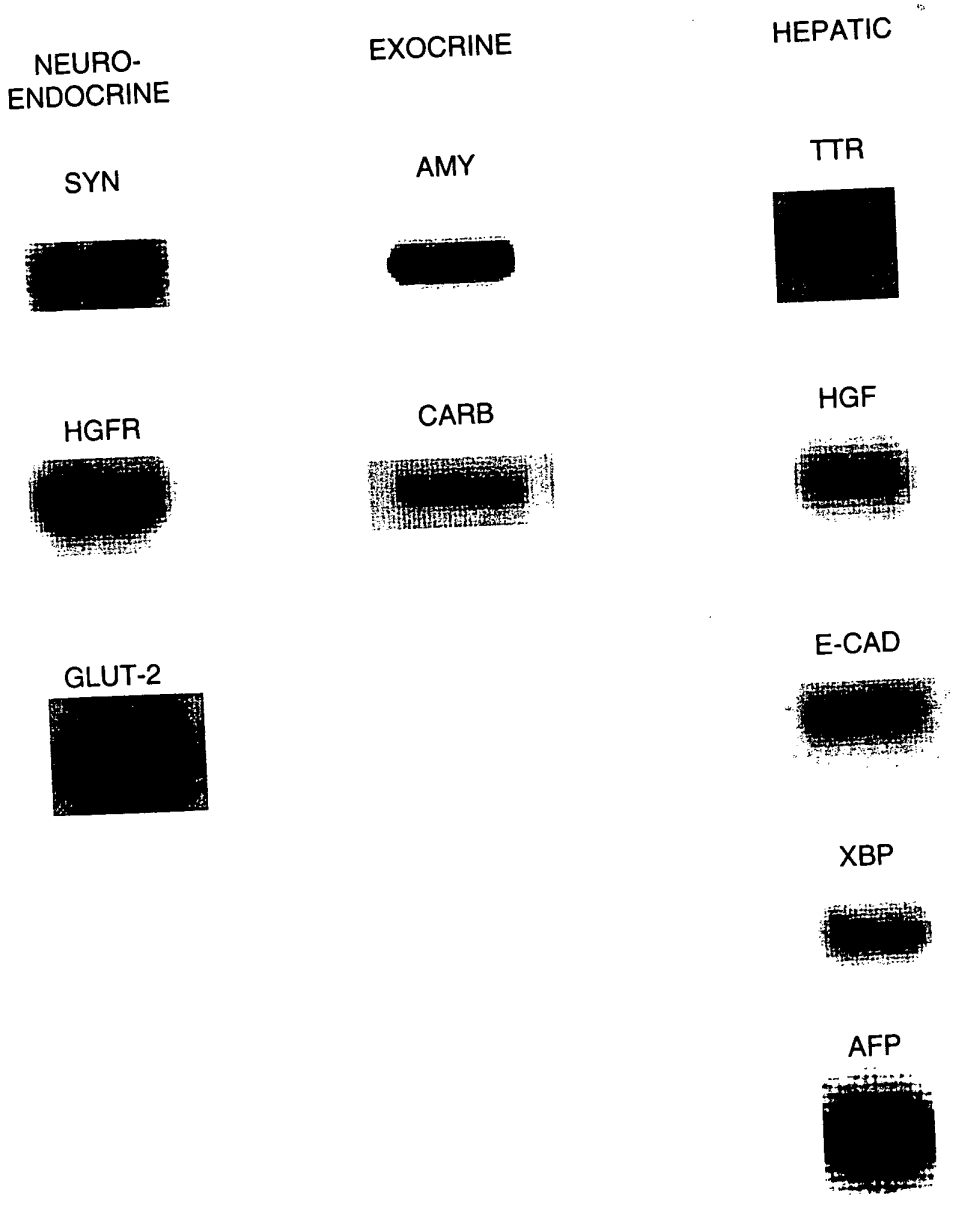

NEURO-
ENDOCRINE
EXOCRINE
HEPATIC
SYN
AMY
TTR
HGFR
CARB
HGF
GLUT-2
E-CAD
XBP
AFP

FIG. 16

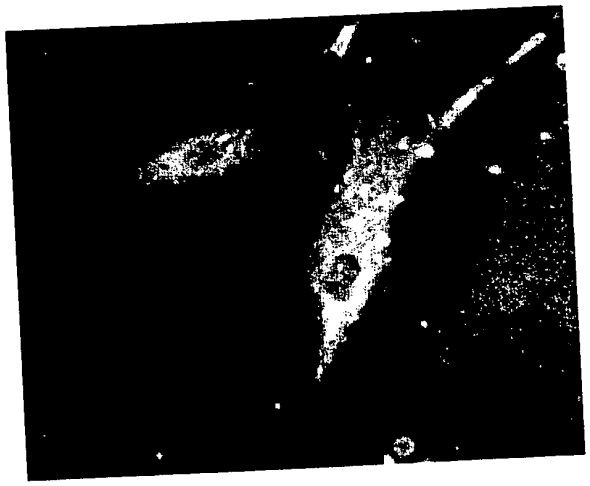
Figure 17

SEQ ID NO: 3

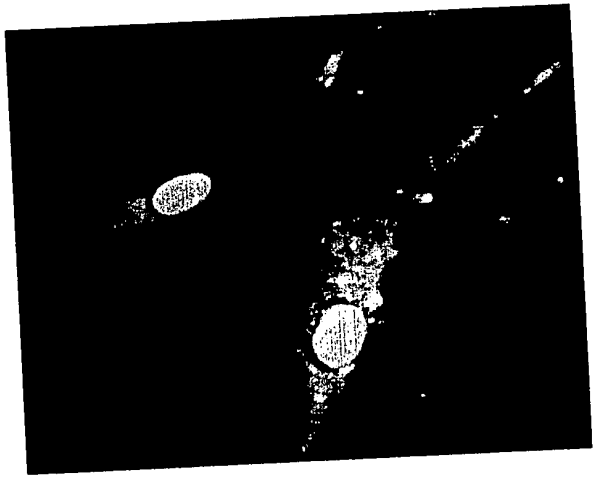
atggccggcgcccccggcccgctgcgccttgcgctgctgctcgggatggtgggcagggccggcccccgcccccagggtgccactg
tgtccctctgggagacggtgcagaaatggcgagaataccgacgccagtgccagcgctccctgactgaggatccacctcctgccacagact
tgttctgcaaccggaccttcgatgaatacgcctgctggccagatggggagccaggctcgttcgtgaatgtcagctgcccctggtacctgccc
tgggccagcagtgtgccgcagggccacgtgtaccggttctgcacagctgaaggcctctggctgcagaaggacaactccagcctgccctg
gagggacttgtcggagtgcgaggagtccaagcgaggggagagaagctccccggaggagcagctcctgttcctctacatcatctacacgg
tgggctacgcactctccttctctgctctggttatcgcctctgcgatcctcctcggcttcagacacctgcactgcaccaggaactacatccacct
gaacctgtttgcatccttcatcctgcgagcattgtccgtcttcatcaaggacgcagccctgaagtggatgtatagcacagccgcccagcagc
accagtgggatgggctcctctcctaccaggactctctgagctgccgcctggtgtttctgctcatgcagtactgtgtggcggccaattactactg
gctcttggtggagggcgtgtacctgtacacactgctggccttctcggtcttctctgagcaatggatcttcaggctctacgtgagcataggctgg
ggtgttcccctgctgtttgttgtcccctggggcattgtcaagtacctctatgaggacgagggctgctggaccaggaactccaacatgaactac
tggctcattatccggctgcccattctctttggcattggggtgaacttcctcatctttgttcgggtcatctgcatcgtggtatccaaactgaaggcc
aatctcatgtgcaagacagacatcaaatgcagacttgccaagtccacgctgacactcatcccccctgctggggactcatgaggtcatctttgcc
tttgtgatggacgagcacgcccgggggacccctgcgcttcatcaagctgtttacagagctctccttcacctccttccaggggctgatggtggcc
atcttatactgctttgtcaacaatgaggtccagctggaatttcggaagagctgggagcgctggcggcttgagcacttgcacatccagaggga
cagcagcatgaagcccctcaagtgtcccaccagcagcctgagcagtggagccacggcgggcagcagcatgtacacagccacttgccag
gcctcctgcagctgagactccagcgcctgccctccctggggtccttgctgcaggccgggtggccaatccaggagaagcagcctcctaatttt
gatcacagtggcgagaggagaggaaaaacgatcgctgtgaaaatgaggaggattgcttcttgtgaaaccacaggccccttggggttccccc
agacagagccgcaaatcaaccccagactcaaactcaaggtcaacggcttattagtgaaactggggcttgcaagaggaggtggttctgaaa
gtggctcttctaacctcagccaaacacagagcgggagtgacgggagcctcctctgcttgcatcacttggggtcaccaccctcccctgtcttct
ctcaaagggaagctgtttgtgtgtctgggttgcttatttccctcatcttgccccctcatctcactgcccagtttctttttgaggggctttgtttgggcc
actgccagcagctgtttctggaaatggctgtaggtggtgttgagaaagaatgagcattgagacggtgctcgcttctcctccaggtatttgagtt
gttttggtgcctgcctctgccatgcccagagaatcagggcaggcttgccaccggggaacccagccctggggtatgagctgccaagtctattt
taaagacgctcaagaatcctctggggttcatctagggacacgttaggaatgtccagactgtgggtgtagattacctgccacttccaggagcc
cagagggccaagagagacattgcctccacctctccttggaaatactttatctgtgaccacacgctgtctcttgagaatttggatacactctctag
ctttaggggaccatgaagagactctcttagggaaaccaatagtccccatcagcaccatggaggcaggctccccctgcctttgaaattccccc
acttgggagcttgtatatacttcactcacttttctttattgctgtgaatagtctgtgtgcacaatgggcaattctgacttctcccatctagtggaaatg
agcgaaatcatggttgtagtgatgttg

SEQ ID NO: 4

MAGAPGPLRLALLLLGMVGRAGPRPQGATVSLWETVQKWREYRRQCQRSLTEDPPPA
TDLFCNRTFDEYACWPDGEPGSFVNVSCPWYLPWASSVPQGHVYRFCTAEGLWLQKD
NSSLPWRDLSECEESKRGERSSPEEQLLFLYIIYTVGYALSFSALVIASAILLGFRHLHCTR
NYIHLNLFASFILRALSVFIKDAALKWMYSTAAQQHQWDGLLSYQDSLSCRLVFLLMQ
YCVAANYYWLLVEGVYLYTLLAFSVFSEQWIFRLYVSIGWGVPLLFVVPWGIVKYLYE
DEGCWTRNSNMNYWLIIRLPILFGIGVNFLIFVRVICIVVSKLKANLMCKTDIKCRLAKST
LTLIPLLGTHEVIFAFVMDEHARGTLRFIKLFTELSFTSFQGLMVAILYCFVNNEVQLEFR
KSWERWRLEHLHIQRDSSMKPLKCPTSSLSSGATAGSSMYTATCQASCS



GLP-1R



GLP-1R/NUC

PRE-IMM

NESTIN

Figure 18A

Figure 18

B

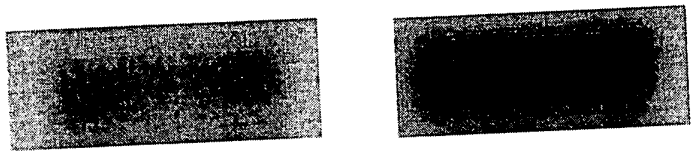


Figure 19

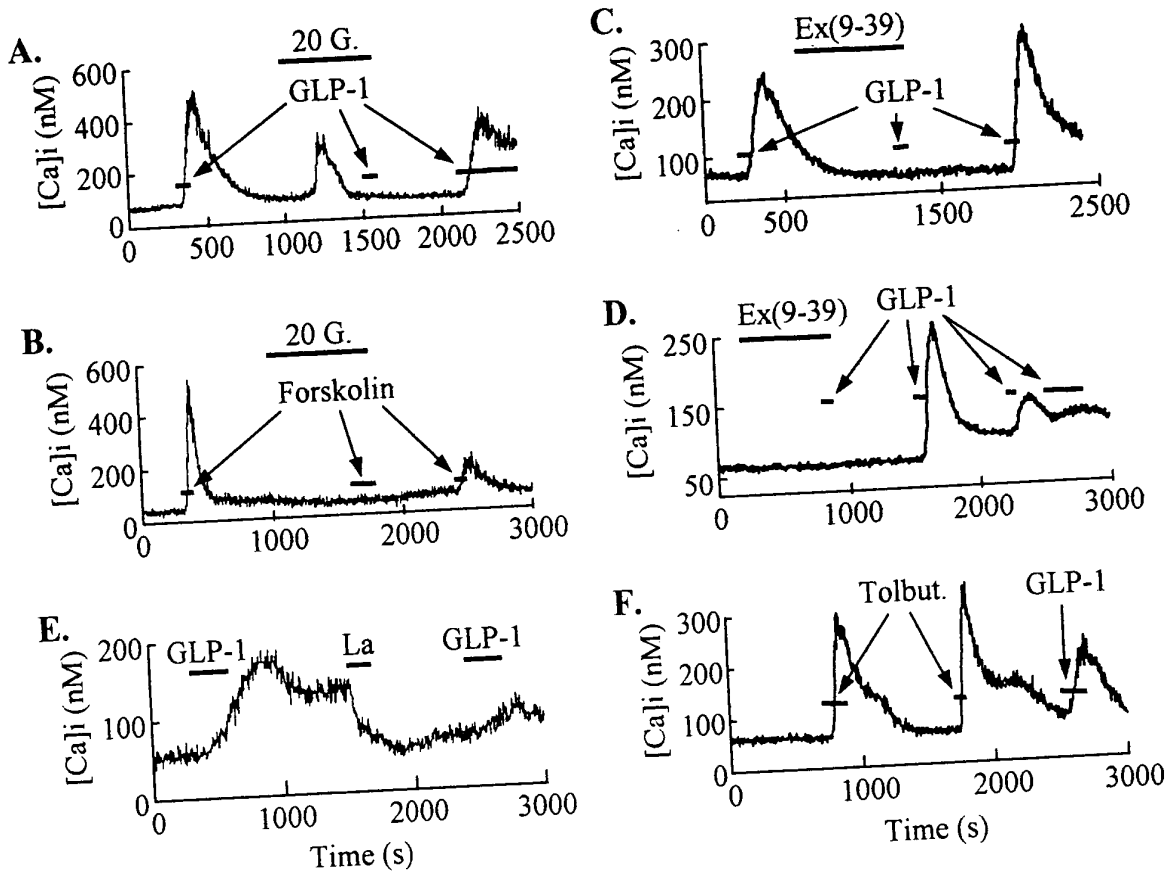
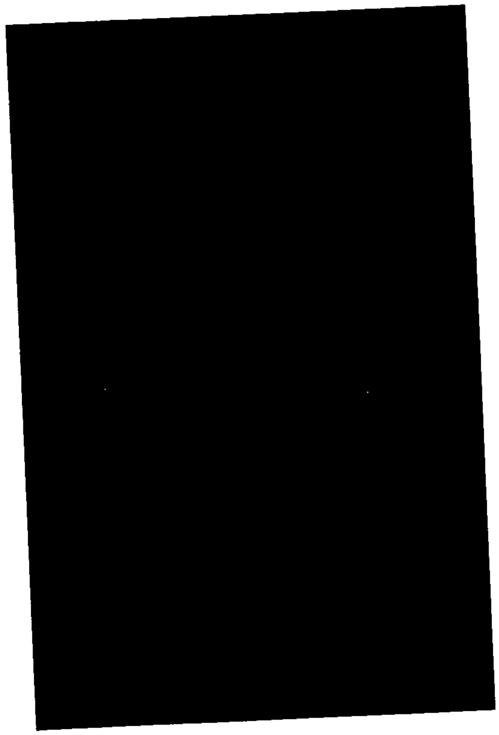


Figure GLP-1(7-36)amide and Tolbutamide stimulate $[Ca^{2+}]_i$ influx in stem cells.

(A) Fura 2 loaded cells bathed in 5.6 mM glucose show a $[Ca^{2+}]_i$ increase in response to 10 nM GLP-1. Increasing the extracellular glucose to 20 mM (20 G) also caused an increase of $[Ca^{2+}]_i$ but application of GLP-1 in 20 mM glucose failed to produce a $[Ca^{2+}]_i$ response. A third application of GLP-1 on returning to 5.6 mM glucose produced a $[Ca^{2+}]_i$ response. **(B)** The glucose-dependent effects of GLP-1 were reproduced by 10 mM forskolin, suggesting that $[Ca^{2+}]_i$ elevation is cAMP-mediated. **(C)** The GLP-1 mediated increase of $[Ca^{2+}]_i$ was reversibly inhibited by 10 nM exendin (9-39). This effect is not due to receptor desensitization **(D)** as application of GLP-1 in the presence of exendin (9-39) failed to produce a response whereas subsequent applications of GLP-1 after washout of exendin produced repeated $[Ca^{2+}]_i$ elevations. **(E)** The GLP-1-mediated increase of $[Ca^{2+}]_i$ is inhibited by 0.5 mM extracellular La^{3+}, suggesting that GLP-1 stimulates Ca^{2+} influx. **(F)** Stem cells bathed in 5.6 mM glucose were stimulated with 100 μM tolbutamide (Tolbut.) and respond to repeated applications with increases in $[Ca^{2+}]_i$. Application of 10 nM GLP-1 also stimulates an increase of $[Ca^{2+}]_i$ suggesting that GLP-1 acts by depolarizing the cells.

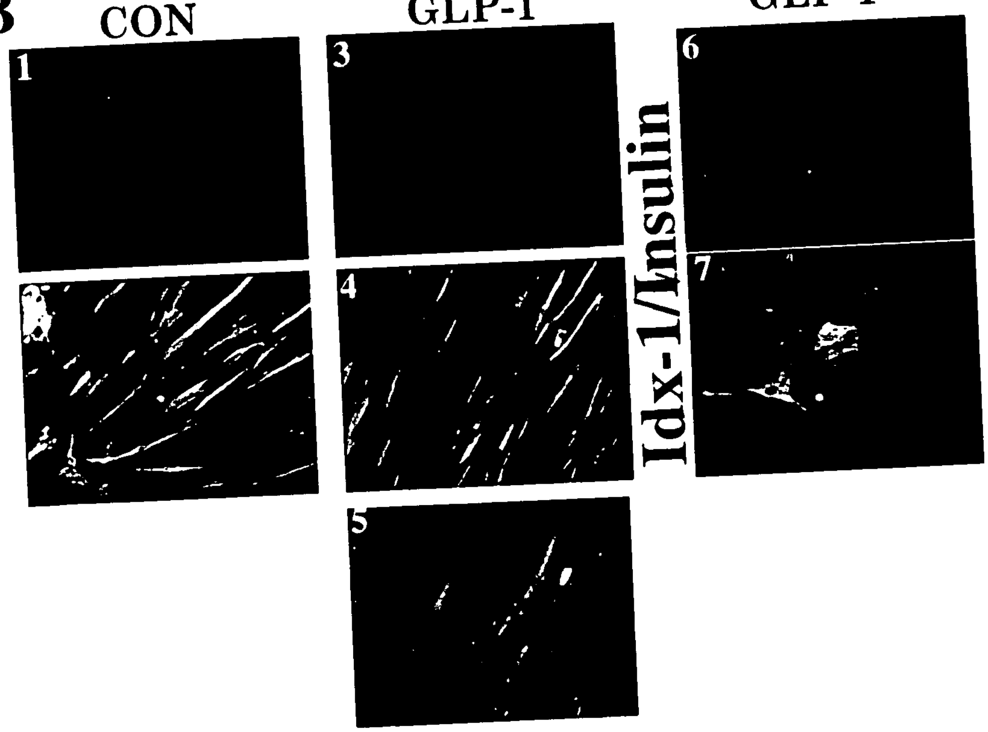
Figure 20

A



Nestin/Insulin

B



CON
GLP-1
GLP-1
Nestin/Insulin
Idx-1/Insulin
1
2
3
4
5
6
7

Figure 21

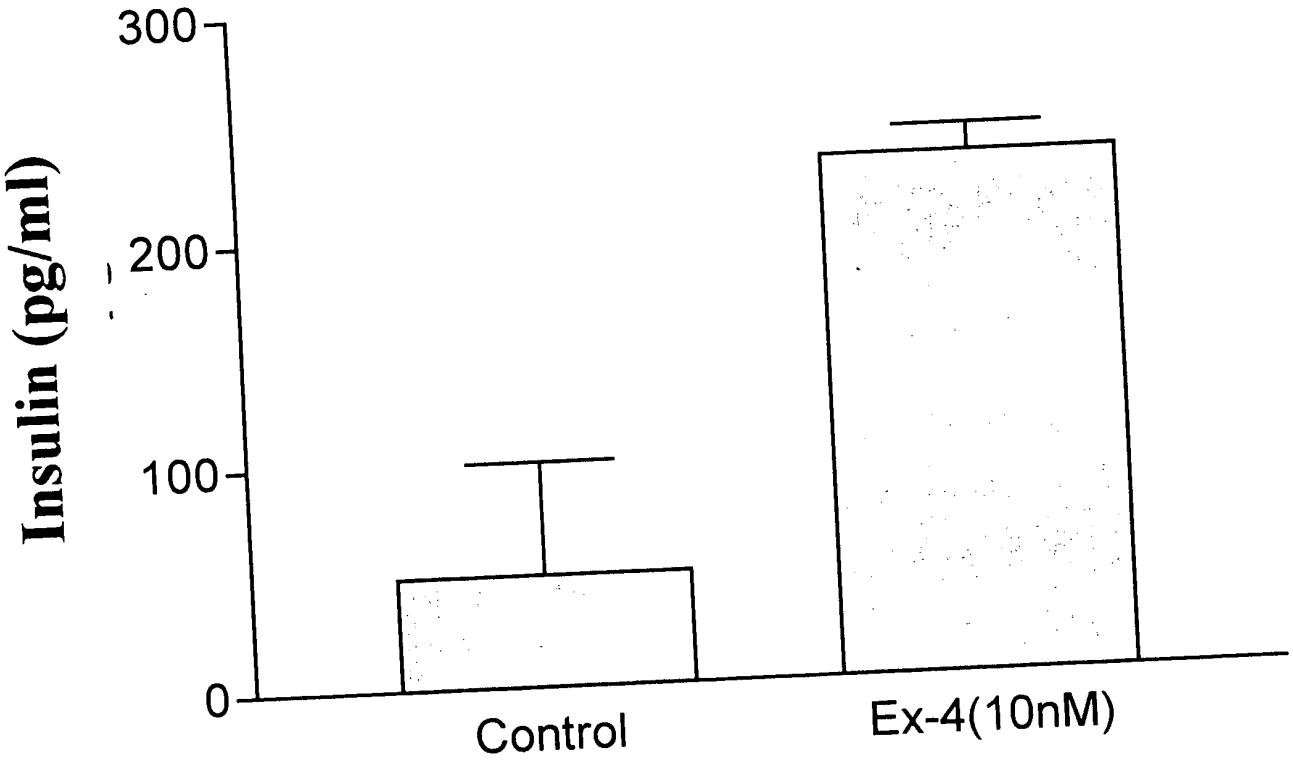


Figure 22

A

Transfected with hIDX-1 and incubated with GLP-1 (7-36)

B

Transfected with hIDX-1 and incubated with Vehicle (PBS)

Insulin/ IDX